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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/822,254	04/09/2004	Shahriar Shane Taremi	JB06017US01	1701
24265	7590	08/08/2006	EXAMINER	
SCHERING-PLOUGH CORPORATION PATENT DEPARTMENT (K-6-1, 1990) 2000 GALLOPING HILL ROAD KENILWORTH, NJ 07033-0530			STEADMAN, DAVID J	
			ART UNIT	PAPER NUMBER
			1656	

DATE MAILED: 08/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/822,254

Applicant(s)

TAREMI ET AL.

Examiner

David J. Steadman

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 24 February 2006 and 26 May 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2,14-17,21-23 and 26-30 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 14 is/are allowed.
- 6) ☒ Claim(s) 1,2,15-17,21-23 and 26-30 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

- [1] Claims 1-2, 14-17, 21-23, and 26-30 are pending in the application.
- [2] Applicant's amendments to the claims, filed on 2/24/2006 and 5/26/2006, are acknowledged. The claim listing filed on 2/24/2006 fails to satisfy the requirements of 37 CFR 1.121 for the reason(s) set forth in the Office communication mailed on 5/16/2006. The claim listing filed on 5/26/2006 replaces all prior versions and listings of the claims.
- [3] Receipt of a substitute Declaration by Inventor Duca, filed on 2/24/2006, is acknowledged.
- [4] Receipt of a Petition under 37 CFR § 1.48(a)(1) to add inventor Yaolin Wang, filed on 3/7/2006, is acknowledged.
- [5] Applicant's arguments filed on 2/24/2006 have been fully considered and are deemed to be persuasive to overcome some of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.
- [6] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Correction of Inventorship

- [7] In view of the papers filed on 2/24/2006, it has been found that this nonprovisional application, as filed, through error and without deceptive intent, improperly set forth the inventorship, and accordingly, this application has been

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corrected in compliance with 37 CFR 1.48(a). The inventorship of this application has been changed by adding inventor Yaolin Wang.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of Office records to reflect the inventorship as corrected.

Examiner Comment/Clarification

[8] According to the sequence listing, the "seven variable positions" of SEQ ID NO:4 can be replaced only by certain amino acids (sequence listing filed on 4/9/2004 at pp. 3-4). Applicant confirms this by stating "the amino acids that can be placed in variable positions are not unlimited, but, rather, are specifically identified (see Sequence Listing at SEQ ID NO:4 and Table 1 (page 24, lines 10-11))" (instant response at p. 11, middle). Thus, the polypeptide of claims 1, 15, and 16 has been interpreted as being limited to having those amino acids at the "seven variable positions" of SEQ ID NO:4 as defined at p. 3 of the sequence listing filed on 4/9/2004.

Claim Objections

[9] Claims 26-27 are objected to in the recitation of "polypeptide consists of the amino acid of SEQ ID NO:". It is suggested that the term "sequence" be inserted following "the amino acid."

Claim Rejections - 35 USC § 112, Second Paragraph

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[10] Claims 1, 15-16, 21-23, and 29-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[a] Claims 1, 15, and 16 (claims 21-23 dependent therefrom) are indefinite in the recitation of "soluble at a 34 mg/ml concentration" as it is unclear as to solvent in which the polypeptide is solvated at the recited concentration. A skilled artisan would recognize that the solubility of a protein is dependent upon the solvent used. A polypeptide that is soluble in a first solvent to a particular concentration may not be soluble in a second solvent to that concentration. Thus, it is unclear as to the scope of recited polypeptides that are "soluble at a 34 mg/ml concentration." It is suggested that applicant clarify the meaning of the phrase "soluble at a 34 mg/ml concentration."

[b] It is unclear from claims 29-30 as to whether the phrase "characterized by the structural coordinates..." is intended as being directed to the *polypeptide* of the crystal of claim 28 or the *crystal itself*. If applicant intends for the phrase to be directed to the crystal and not the polypeptide of the crystal, it is noted that the structural coordinates of Tables 3 and 4 appear to be the structural coordinates of a *polypeptide*, and not a crystal. It is suggested that applicant clarify the meaning of the term. In the interest of advancing prosecution, the examiner has interpreted the phrase as being directed to the polypeptide of the crystal.

Claim Rejections - 35 USC § 112, First Paragraph

[11] Claim(s) 1-2, 15-17, 21-23, and 26-27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

MPEP § 2163 states, "when filing an amendment an applicant should show support in the original disclosure for new or amended claims" (MPEP 8th Ed., October 2006 Revision at pp. 2100-176 and 2100-183) and "[i]f the originally filed disclosure does not provide support for each claim limitation, or if an element which applicant describes as essential or critical is not claimed, a new or amended claim must be rejected under 35 U.S.C. 112, para. 1, as lacking adequate written description."

In the amendment filed on 2/24/2006, applicant points to pp. 4, 5, and 46 of the specification as providing written support for the amendment to claim 1. However, while the cited disclosure would appear to provide support for the "species" of a HDM2(F55Y/Y76H) protein-tripeptide complex solubilized to 34 mg/ml in 25 mM Hepes-potassium hydroxide, pH7.5, 0.15 M potassium chloride, 1 mM EDTA, 0.03% sodium azide and 5 mM DTT buffer, this single species as disclosed in the specification fails to provide written support for the "genus" of proteins as encompassed by the claims. It is suggested that applicant show support in the original application for the limitation at issue.

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[12] The written description rejection of claim(s) 16-17, 21-23, and 26-30 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a prior Office action.

RESPONSE TO ARGUMENT: Applicant argues (in relevant part) that unit cell dimensions, while being a “useful means by which to describe a particular crystal,” are not the only way to comply with the description requirement. According to applicant, the invention should not be limited to the disclosed species of crystal as defined by unit cell dimensions as this would be unduly limiting. Applicant argues the amino acid sequence of a crystallized polypeptide is sufficient for describing the crystal itself and that issued US patents describe polypeptide crystals using means other than unit cell dimensions.

Applicant's argument is not found persuasive. The examiner agrees with applicant's assertion that description of a genus of crystals is not limited to recitation of unit cell dimensions. However, the crystal must nonetheless be described such that a skilled artisan would recognize that applicant was in possession of the claimed invention at the time of filing. In this case, the examiner maintains the position that the two disclosed species of crystals (specification at pp. 46 and 63) fail to describe all crystals as encompassed by the claimed genus. According to applicant, the amino acid sequence of a crystallized protein is sufficient to describe the structural characteristics and features of all members of the genus of claimed crystals. However, according to this logic, one must only describe the primary structure of a polypeptide in order to describe a crystal thereof. However, the primary structure of a polypeptide is insufficient to describe even a single distinguishing identifying characteristics of a *crystal* of that

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polypeptide, particularly as there is no way to predict *a priori* the resulting structure of a crystal based upon the primary structure of a polypeptide or even based on crystals of structurally related polypeptides. For example, the reference of Kierzek et al. [(2001) *Biophys Chem* 91:1-20] teaches "each protein crystallizes under a unique set of conditions that cannot be predicted from easily measurable physico-chemical properties...crystallization conditions must be empirically established for each protein to be crystallized" (p. 2, left column, top). The teachings of Kierzek et al. are evidenced by the reference of Buts *et al.* (*Acta Crystallogr. D.* 61:1149-1159), which teaches that "[f]ive naturally occurring variants, differing in 1-18 amino acids, of the 177-residue lectin domain of the F17G fimbrial adhesin were expressed and purified in identical ways. For four out of the five variants crystals were obtained, mostly in non-isomorphous space groups" and that crystallization of protein variants that differed from a parent sequence by only a single amino acid resulted in different crystal forms with distinct diffraction properties (see Tables 1-3). See also applicant's own specification, which shows that even a single amino acid difference between two polypeptides can result in crystals having distinct unit cell dimensions (compare the unit cell dimensions of SEQ ID NO:6 and 10 at p. 46 and 63 of the specification). As such, the genus of claimed crystals encompasses species having widely variant species, encompassing species having any space group and unit cell dimensions, which is undisputed by applicant. According to MPEP § 2163, "when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus." In this case, the recitation of amino acid sequence alone fails to reflect the variation among the species

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of claimed crystals, which encompasses species optionally bound to any ligand and having any distinguishing identifying characteristics, e.g., any space group and unit cell dimensions. Even assuming *arguendo* the amino acid sequence of a polypeptide was sufficient to describe a genus of crystals, it is noted that the polypeptide of the crystal of claims 28-30 is widely variant in structure because the polypeptide is merely "characterized by" the structure coordinates of Table 3 or 4. Furthermore, it is noted that the specification fails to disclose even a single representative species of a crystal that can diffract x-rays to a resolution greater than 1.5 Angstroms as required by claim 23.

Given the lack of description of a representative number of crystals, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[13] The scope of enablement rejection of claim(s) 16-17, 21-23, and 26-30 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a prior Office action.

RESPONSE TO ARGUMENT: Applicant argues (in relevant part) the claimed crystals can be made without undue experimentation using standard techniques and the specification for guidance, particularly Examples 2 and 3 at pp. 45 and 63, respectively.

Applicant's argument is not found persuasive. The examiner maintains the position that the specification, while being enabling for a crystal of the purified polypeptide of SEQ ID NO:10 co-crystallized with SCH549128 having the space group

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symmetry $P2_12_12_1$ and the unit cell dimensions of $a=37.999 \text{ \AA}$, $b=45.333 \text{ \AA}$, $c=63.999 \text{ \AA}$, $\alpha=\beta=\gamma=90^\circ$ that diffracts x-rays to a resolution of 1.70 \AA and a crystal of the purified polypeptide of SEQ ID NO:6 co-crystallized with $\text{Ac-}^{60}\text{I} \text{WAC}_{30}\text{E}$ having the space group symmetry $P2_12_12_1$ and the unit cell dimensions of $a=41.1 \text{ \AA}$, $b=42.7 \text{ \AA}$, $c=53.777 \text{ \AA}$, $\alpha=\beta=\gamma=90^\circ$ that diffracts x-rays to a resolution of 2.1 \AA ; does not reasonably provide enablement for all crystals as encompassed by the claims. It appears that applicant takes the position that the crystallization conditions used in Examples 2 and 3 can be used to crystallize other polypeptides optionally complexed with any other ligand as broadly encompassed by the claims optionally to a resolution greater than 1.5 Angstroms. However, as noted in the prior Office action, the state of the art at the time of the invention acknowledges a high level of unpredictability for making the full scope of claimed crystals. For example, the reference of Branden et al. ("Introduction to Protein Structure Second Edition", Garland Publishing Inc., New York, 1999; cited in the prior Office action) teaches that "[c]rystallization is usually quite difficult to achieve" (p. 375). In view of the use of the claimed crystal for generating a three-dimensional structure, it is noted that the claimed crystals should be of diffraction quality, having a well-ordered structure. Branden et al. teaches that "[w]ell-ordered crystals...are difficult to grow because globular protein molecules are large, spherical, or ellipsoidal objects with irregular surfaces, and it is impossible to pack them into a crystal without forming large holes or channels between the individual molecules" (p. 374). Applicant does not dispute these teachings. The prior art further acknowledges a high level of unpredictability in applying crystallization parameters for a first polypeptide to a second

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polypeptide. For example, the reference of Kierzek et al. [(2001) *Biophys Chem* 91:1-20] teaches "[t]he growth of large and well ordered protein crystals remains the major obstacle in protein structure determination by means of X-ray crystallography" (p. 1, abstract) and that "[t]he reason for this is that each protein crystallizes under a unique set of conditions that cannot be predicted from easily measurable physico-chemical properties...crystallization conditions must be empirically established for each protein to be crystallized" (p. 2, left column, top). The teachings of Kierzek et al. are evidenced by the reference of Buts et al. (*Acta Crystallogr. D.* 61:1149-1159), which teaches that "[f]ive naturally occurring variants, differing in 1-18 amino acids, of the 177-residue lectin domain of the F17G fimbrial adhesin were expressed and purified in identical ways. For four out of the five variants crystals were obtained, mostly in non-isomorphous space groups, with diffraction limits ranging between 2.4 and 1.1 Å resolution" and that crystallization of protein variants that differed from a parent sequence by only a single amino acid resulted in different crystal forms with distinct diffraction properties (see Tables 1-3). See also applicant's own specification, which shows that different crystallization conditions were required for crystallization of SEQ ID NO:6 and 10 (compare the crystallization conditions for SEQ ID NO:6 and 10 at pp. 46 and 63 of the specification). In view of the cited teachings, a skilled artisan would recognize the high level of unpredictability in applying the disclosed crystallization conditions with an expectation of obtaining diffraction-quality crystals. In this case, the specification provides only two working examples of the claimed crystals, i.e., a crystal of the purified polypeptide of SEQ ID NO:10 co-crystallized with SCH549128 having the space group

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symmetry $P2_12_12_1$ and the unit cell dimensions of $a=37.999 \text{ \AA}$, $b=45.333 \text{ \AA}$, $c=63.999 \text{ \AA}$, $\alpha=\beta=\gamma=90^\circ$ that diffracts x-rays to a resolution of 1.7 \AA and a crystal of the purified polypeptide of SEQ ID NO:6 co-crystallized with $\text{Ac-}^{60}\text{I} \text{WAC}_{30}\text{E}$ having the space group symmetry $P2_12_12_1$ and the unit cell dimensions of $a=41.1 \text{ \AA}$, $b=42.7 \text{ \AA}$, $c=53.777 \text{ \AA}$, $\alpha=\beta=\gamma=90^\circ$ that diffracts x-rays to a resolution of 2.1 \AA . The specification fails to provide guidance regarding application of the disclosed crystallization conditions or modifications thereof to crystallization of other polypeptides as encompassed by the claims, *i.e.*, all mutants as encompassed by SEQ ID NO:4 or polypeptides that are “characterized by” structure coordinates of Table 3 or 4, optionally complexed with any compound that result in diffraction-quality crystals. Further, the specification fails to provide guidance regarding crystallization to obtain a more ordered crystal that will diffract x-rays to 1.5 \AA . While methods of protein crystallization were known in the art at the time of the invention, it was *not* routine in the art to screen – by a trial and error process – to crystallize a vast number proteins optionally complexed with any ligand under any crystallization conditions to make all crystals as broadly encompassed by the claims. Thus, in view of the analysis of the Factors of *In re Wands*, the specification fails to enable a skilled artisan to make all crystals as encompassed by the claims.

Claim Rejections - 35 USC § 102

[14] The rejection of claim(s) 28-31 under 35 U.S.C. 102(b) as being anticipated by Kussie et al. (*Science* 274:948-953; cited in the IDS filed 8/30/2004) and the rejection of claim(s) 28-31 under 35 U.S.C. 102(e) as being anticipated by Schubert et al. (US

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Patent Application Publication 2004/0197893) are withdrawn in view of applicant's amendment to claim 28 to limit the compound of the crystallized complex to Ac-⁶³ClWAC₃CE and cancellation of claim 31.

Conclusion

[15] Status of the claims:

- Claims 1-2, 14-17, 21-23, and 26-30 are pending.
- Claim 14 appears to be in condition for allowance.
- Claims 1-2, 15-17, 21-23, and 26-30 are rejected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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A handwritten signature in black ink, appearing to read 'D. Steadman', with a stylized flourish at the end.

David J. Steadman, Ph.D.
Primary Examiner
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